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(54) Title: SURFACE ACTIVE VISCOELASTIC SOLUTIONS FOR OCULAR USE

(57) Abstract

This invention encompasses a modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising a pharmaceutical grad viscoelastic fraction selected form a group consiting of an acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms and mixtures of said acyl-substituted hyaluronic acid with hyaluronic acid, and hydroxypropylmethylcellulose. In particular these solutions have a surface tension of between 40 and 65 dynes/cm^2; particularly a viscoelastic fraction has an average molecular weight of at least 50,000. In some embodiments a physiological buffer fraction is present. This invention further encompasses a method of using the claimed composition.

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SURFACE ACTIVE VISCOELASTIC SOLUTIONS FOR OCULAR USE

This application is a continuation-in-part of copending U.S. Pat. App. 08/061,773 filed May 13, 1993, which is a continuation of U.S. Pat. App. 07/440,078 filed November 22, 1989, now abandoned.

Field of the Invention.

The present invention relates to ophthalmic solutions for use during ocular and intraocular surgery, and more particularly to the use of surface active viscoelastic solutions during the extraction of a cataractous human lens and the implantation of a prosthetic ocular and intraocular lens. During surgery, the use of ophthalmic infusions with controlled physical properties, especially surface activity and viscoelastic properties, is advantageous for (1) replacing the fluid aqueous humor or ocular and intraocular air, (2) protecting the internal structures of the eye from accidental instrument or ocular and intraocular prosthetic device contact, (3) preventing irrigation damage by solutions used in routine cataract surgery, and (4) retarding aspiration from the eye of the viscoelastic solution during the surgical procedure. In addition, the invention relates to a method of adhering a contact lens to the surface of the eye, such as in association with procedures permitting a medical professional to view ocular and intraocular structures through the contact lens and through the viscoelastic solution. In

another application, the viscoelastic solution of this invention is used by injecting the solution into or under tissues within the eye, such as to dissect tissue off of the retina.

Background of the Invention

In the past, biocompatible polymers used in ocular and intraocular surgery have been the naturally occurring mucopolysaccharides hyaluronic acid and chondroitin sulfate; mixtures of hyaluronic acid and chondroitin sulfate; and, cellulose derivatives, such as hydroxypropylmethylcellulose (HPMC). Table 1 presents data reported in Viscoelastic Materials, Ed. E.S. Rosen, Proceedings of the Second International Symposium of the Northern Eye Institute, Manchester [U.K.], 17-19 July, 1986 (Pergamon Press, New York) as to the molecular weight of commercially available ocular products. Depending on the source from which these mucopolysaccharides are drawn, the molecular weights are estimated in the 50,000 range with the hyaluronic acid extending upwards to the 8×10^6 range. Hyaluronic acid was first isolated and characterized by Meyer, Palmer and reported in the J. Biol. Chem., Vol. 107, p. 629 (1934) and Vol. 114, p.689 (1936) and by Balazs in the Fed. Proc. Vol. 17, p. 1086 (1958); and chondroitin sulfate by Bray et al. in Biochem. J. Vol. 38, p. 144 (1944); and Patat, Elias, Z. Physiol. Chem. vol. 316, p. 1 (1959).

Literature in the art describes the basic isolation and characterization of the viscoelastic solutions. It is a surprising feature of this invention which describes the control

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of viscoelastic properties as related to the surface activity, or the solution fracturing under applied stress. In particular, it is surprising to manipulate or enhance the physical properties of viscoelastic solutions of mucopolysaccharides, hyaluronic acid, and/or chondroitin sulfate. It is believed that disclosure here of a processes to provide hyaluronic acid and species thereof with controlled surface activity is unique. This is also especially true of the control of surface activity of mucopolysaccharide solutions by the addition of biologically compatible surfactants. A characteristic feature of biologically compatible surfactants is the absence of observed alteration in cellular physiology upon contact. Early work in the viscoelastic field was presented by the inventor of this disclosure and his associates. Benedetto, D.A. et. al., Viscoelastic Materials: Basic Science and Clinical Application, (Symposium Proceedings), University of Manchester, England, July 17-19, 1986.

As to commercial production, a review of the ophthalmic pharmacopoeia reveals there are several viscoelastic solutions produced for ocular and intraocular use during ophthalmic surgery. The most common application for these solutions is in the intraocular lens implant procedure for human cataract surgery. This procedure involves extraction of the cataractous human lens through a small surgical opening in the eye and the replacement of the lens by a prosthetic intraocular lens placed in situ. Biocompatible polymers presently or previously in use are hyaluronic acid (Healon™, Amvisc™); chondroitin sulfate, and

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a combined solution of hyaluronic acid and chondroitin sulfate (Viscoat™); and a hydroxypropylmethylcellulose solution (Occucoat™). Research conducted recently demonstrates that Healon™ and Amvisc™ are not surface active, but Viscoat™ and Occucoat™ are.

Chondroitin sulfate does not exist as a free polysaccharide in its native state, but as a proteoglycan. It is obtained from sources associated with protein contaminants. The avoidance of chondroitin sulfate avoids a potential source of pyrogenic reaction, and the substantial cost associated with protein removal.

Summary of the Invention

The invention presented herein discloses modified mucopolysaccharide or viscoelastic solutions for use as biologically active therapeutic infusions. In one form of the invention, the mucopolysaccharide solution is formed from a viscoelastic fraction and a buffer fraction. It has been found that when a new synthetic molecule acyl-substituted hyaluronic acid is employed as the viscoelastic fraction, control of surface activity is achieved. An indicia of this is the decrease of the surface tension of the solution which is now within predetermined limits discussed below. Surface tension modification is also accomplished with viscoelastic fractions in which the acyl-substituted hyaluronic acid is mixed with one or more of hyaluronic acid; and hydroxypropylmethylcellulose. In certain applications, the viscoelastic solution of this invention is used in a method of adhering a contact lens to the

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surface of the eye, such as in association with procedures permitting a medical professional to view ocular and intraocular structures through the contact lens and through the viscoelastic solution. This is particularly useful in facilitating surgical procedures. In another application, the viscoelastic solution of this invention is used by injection the solution into or under structures or tissues within the eye, such as to dissect tissue off of the retina.

In the broadest terms, surface active viscoelastic solutions with controlled solution properties, are characterized by surface tension, equilibrium contact angle, dynamic viscosity, and cohesiveness (the measure of solution fracture under stress). In a particular embodiment, this invention is delimited by the three dimensional representation of Fig. 7.

In one example, bioengineered hyaluronic acid from a bacterial source with an average molecular weight of 50,000 is modified by acyl substitution with three to twenty carbon atom acyl groups so that the resultant surface tension of such a solution is between 40 and 65 dynes/cm^2. In the practice of this invention, a viscoelastic solution having a surface tension of less than about 56 dynes/cm^2, and more particularly, less than about 50 dynes/cm^2 is of particular advantage.

This invention comprises a modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising:

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a pharmaceutical grade viscoelastic fraction selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof, and absent chondroitin sulfate said fraction having a surface tension of between 40 and 65 dynes/cm^2; and,

optionally with a physiological buffer fraction, such that the viscoelastic comprises about a 0.1% percent of the solution to about 5% of the solution, by weight, and preferably from about 0.5 % to about 3%;

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25°C; and,

optionally wherein the modified mucopolysaccharide solution has a surface tension of less than about 56 dynes/cm^2, and further a surface tension of less than about 50 dynes/cm^2; and further,

optionally wherein the solution has an osmolality of from about 250 to about 400 milliosmoles, or is generally isotonic with ophthalmic tissue.

In some embodiments the modified mucopolysaccharide solution viscoelastic fraction has an average molecular weight of at least 50,000. Reference is further made to the viscoelastic fraction being an acyl-substitute hyaluronic acid having acyl groups thereof with three to twenty carbon atoms.

In particular applications the modified mucopolysaccharide solution of this invention includes a surfactant fraction of a biocompatible component selected from a group consisting of

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phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants, with the surfactant present in an amount sufficient to produce the required surface tension. In particular, a biological surfactant fraction of a free fatty acid is present in an amount of less than 1 mg/ml. Further embodiments include a surfactant fraction of a biocompatible component selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants, said surfactant present in an amount less than 10 micrograms/ml. In a preferred embodiment the surfactant fraction of biocompatible component is a free fatty acid.

In a further embodiment the modified mucopolysaccharide solution has a viscoelastic fraction of a mixture of acyl-substituted hyaluronic acid and hyaluronic acid, and particularly with a surfactant fraction of a biocompatible component selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants, with surfactant present in an amount sufficient to produce the required surface tension, usefully in an amount less than 10 micrograms/ml. Preferred surfactants are free fatty acids such as oleic acid.

Particular modified mucopolysaccharide solutions of the invention are characterized by aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, and particularly in a range of 50 to 200 mm Hg, wherein the solution

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is easily fractured. Similarly, those solutions with an aspiration profile of from about horizontal up to about 1.5 and more particularly from about horizontal to about 1.0 are preferred.

In another embodiment this present invention comprises a modified mucopolysaccharide solution for use during ophthalmic surgery for protection of the internal ocular structures including corneal endothelium from accidental touch by surgical instruments, yet permitting of observation of said structures comprising:

an optically clear polymeric fraction of high purity mucopolysaccharides selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof and absent chondroitin sulfate, said fraction having a surface tension of between 40 and 65 dynes/cm^2; and,

optionally a physiological buffer fraction, such that the viscoelastic comprises about a 0.1% percent of the solution to about 5% of the solution, by weight, and preferably from about 0.5 % to about 3%;

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25 C; and,

wherein said mucopolysaccharide fraction has an average molecular weight of at least 50,000; and,

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a biological surfactant fraction of a free fatty acid present in an amount less than 10 micrograms/ml; and,

optionally wherein the modified mucopolysaccharide solution has a surface tension of less than about 56 dynes/cm^2, and further a surface tension of less than about 50 dynes/cm^2.

In some embodiment of this modified mucopolysaccharide solution a particular polymeric fraction is hyaluronic acid.

Particular modified mucopolysaccharide solutions of the invention are characterized by aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, and particularly in a range of 50 to 200 mm Hg, wherein the solution is easily fractured, which optionally include those solutions with an aspiration profile of from about horizontal up to about 1.5 and more particularly from about horizontal to about 1.0.

Another embodiment of the present invention includes a pharmaceutically acceptable modified mucopolysaccharide solution (particularly a surface active mucopolysaccharide) absent chondroitin sulfate having a surface tension of between 40 and 65 dynes/cm^2; and,

a viscosity of between 10,000 and 100,000 centipoise (particularly an average molecular weight of at least 50,000) when measured at a shear rate of 3 sec^{-1} at 25 C.

optionally wherein the modified mucopolysaccharide solution has a surface tension of less than about 56 dynes/cm^2, and further a surface tension of less than about 50 dynes/cm^2.

In this embodiment of a modified mucopolysaccharide solution a particular polymeric fraction is hyaluronic acid.

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In certain applications the mucopolysaccharide solution further comprises a biological surfactant selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants.

Yet a further embodiment of the invention includes a method of protecting internal ocular structures during ocular surgery and retarding aspiration of material from the ocular surgery site by the steps of:

intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution comprising:

a pharmaceutical grade viscoelastic fraction selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof and absent chondroitin sulfate, said fraction with a surface tension of between 40 and 65 dynes/cm^2 (particularly less than about 56 and more particularly less than about 50 dynes/cm^2); and,

optionally a physiological buffer fraction, such that the viscoelastic comprises about a 0.1% percent of the solution to about 5% of the solution, by weight, and preferably from about 0.5 % to about 3%;

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25 C. In such embodiment a

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preferred method entails intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution by a syringe of about 1.13 cm^2 in cross section or less, and optionally about 0.57 cm^2 or less, and further optionally about 0.16 cm^2. In certain embodiments a "sloped" syringe absent sharp reductions in cross sectional area is useful.

Further in this method the invention includes particular modified mucopolysaccharide solutions characterized by aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, and particularly in a range of 50 to 200 mm Hg, wherein the solution is easily fractured. Similarly, those solutions with an aspiration profile of from about horizontal up to about 1.5 and more particularly from about horizontal to about 1.0 are preferred.

An additional embodiment of the invention includes a method of protecting internal ocular structures during ocular surgery by providing a viscoelastic solution that coats ocular structures at a surgical site such that aspiration of the viscoelastic solution is retarded, said method being:

intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution absent chondroitin sulfate and having a surface tension of between 40 and 65 dynes/cm^2 (particularly less than about 56 and more particularly less than about 50 dynes/cm^2); and,

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a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25 C. In such embodiment a preferred method entails intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution by a syringe of about 1.13 cm^2 in cross section or less, and optionally about 0.57 cm^2 or less, and further optionally about 0.16 cm^2.

Further in this method the invention includes particular modified mucopolysaccharide solutions characterized by aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, and particularly in a range of 50 to 200 mm Hg, wherein the solution is easily fractured. Similarly, those solutions with an aspiration profile of from about horizontal up to about 1.5 and more particularly from about horizontal to about 1.0 are preferred.

A next method of the present invention includes a method of protection of internal ocular structures including corneal endothelium from accidental touch by surgical instruments, yet permitting of observation of said structures comprising:

intraocularly introducing a modified mucopolysaccharide solution during ophthalmic surgery wherein said solution comprises

an optically clear polymeric fraction of high purity mucopolysaccharides selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof and absent

chondroitin sulfate, said fraction having a surface tension of between 40 and 65 dynes/cm^2 (particularly less than about 56 and more particularly less than about 50 dynes/cm^2); and,

optionally a physiological buffer fraction, such that the viscoelastic comprises about a 0.1% percent of the solution to about 5% of the solution, by weight, and preferably from about 0.5 % to about 3%;

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25 C; and,

wherein said mucopolysaccharide fraction has an average molecular weight of at least 50,000; and,

a biological surfactant fraction of a free fatty acid present in an amount less than 10 micrograms/ml.

In such embodiment a specific method entails intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution by a syringe of about 1.13 cm^2 in cross section or less, and optionally about 0.57 cm^2 or less, and further optionally about 0.16 cm^2.

Further in this method the invention includes particular modified mucopolysaccharide solutions characterized by aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, and particularly in a range of 50 to 200 mm Hg, wherein the solution is easily fractured. Similarly, those solutions with an aspiration profile of from about horizontal up to about 1.5 and more particularly from about horizontal to about 1.0 are preferred.

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A next embodiment of the invention comprises a modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising:

a pharmaceutical grade viscoelastic fraction selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof, and absent chondroitin sulfate said fraction having a surface tension of between 40 and 65 dynes/cm^2 (particularly less than about 56 and more particularly less than about 50 dynes/cm^2); and,

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25°C.

This invention encompasses a modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising:

a pharmaceutical grade viscoelastic fraction selected from a group consisting of an acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms and mixtures of said acyl-substituted hyaluronic acid with hyaluronic acid, chondroitin sulfate A, chondroitin sulfate B, chondroitin sulfate C, and hydroxypropylmethylcellulose, said fraction with a surface tension of between 40 and 65 dynes/cm^2; particularly a viscoelastic fraction has an average molecular weight of at least 50,000; and,

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optionally a physiological buffer fraction, such that the viscoelastic comprises about a 0.1% percent of the solution to about 5% of the solution, by weight, and preferably from about 0.5 % to about 3%;

whereby, upon infusion of modified mucopolysaccharide solution at the site, the surface activity of the solution enhances coating of the site.

A specific modified mucopolysaccharide solution is one with an acyl-substituted hyaluronic acid, and a preferred viscosity is between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25°C, and optionally further including a surfactant fraction of a biocompatible component selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants, said surfactant present in a trace amount sufficient to produce said surface tension. In one embodiment the surfactant is present in an amount less than 10 micrograms/ml. A preferred surfactant is oleic acid. A preferred modified mucopolysaccharide solution comprises a mixture of an acyl-substituted hyaluronic acid and hyaluronic acid.

In a particular application this invention includes a modified mucopolysaccharide solution for use a biologically compatible therapeutic infusion comprising:

a pharmaceutical grade viscoelastic fraction selected from a group consisting of hyaluronic acid, chondroitin sulfate A, chondroitin sulfate B, and chondroitin sulfate C, said fraction having an average molecular weight of at least 50,000.

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a surfactant fraction of a biocompatible component selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants, said surfactant present in a trace amount sufficient to produce a surface tension of between 40 and 65 dynes/cm^2; and,

optionally a physiological buffer fraction, such that the viscoelastic comprises about a 0.1% percent of the solution to about 5% of the solution, by weight, and preferably from about 0.5 % to about 3%;

whereby, upon infusion of modified mucopolysaccharide solution at the site, the surface activity of the solution enhances coating of the site and results in retardation of aspiration at the site. A preferred modified mucopolysaccharide solution has a viscoelastic fraction of hyaluronic acid, and, optionally, a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1}, and further optionally, a surfactant, particularly oleic acid, and particularly with surfactant present in an amount less than 10 micrograms/ml.

In one embodiment this invention includes a modified mucopolysaccharide solution for use during ophthalmic surgery for protection of the internal ocular structures comprising:

an optically clear polymeric fraction of high-purity mucopolysaccharides and mixtures thereof, said polymeric fraction selected from the group consisting of hyaluronic acid, chondroitin sulfate A, chondroitin sulfate B, chondroitin

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